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(54) **Collagen film for sustained delivery of proteins.**

(57) The present invention relates to single and multiple layer collagen films that are useful for improved sustained release delivery of pharmaceuticals.

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layer, such that said second rate controlling layer is situated at an end of the stack opposite to the end occupied by the first rate controlling layer.

Another aspect of the present invention is a method of enhancing wound healing of an epidermal wound comprising administration of a wound healing effective amount of an active ingredient via a collagen film of the present invention.

Another aspect of the present invention is a method of enhancing wound healing of an internal wound comprising administration of a wound healing effective amount of an active ingredient via a collagen film having two rate controlling layers at opposite ends of a stack.

## DESCRIPTION OF THE DRAWINGS

Figure 1 shows the release rate profile of PDGF from a single layer collagen film (thickness 0.1 mm) made from insoluble collagen fibrils as described in Example 1B.

Figure 2 shows the release rate profile of PDGF from a single layer collagen film (thickness 0.36 mm) made from insoluble collagen fibrils as described in Example 1B.

Figure 3 shows the release rate profile of PDGF from a single layer collagen film (thickness 0.48 mm) made from insoluble collagen fibrils as described in Example 1B.

Figure 4 shows the release rate profile of PDGF from a double layer collagen film (thickness 0.01-3.0 mm) made from soluble collagen as described in Example 2.

Figure 5 shows the release rate profile of PDGF from a four layer collagen film (thicknesses 0.01-3.0 mm) made from soluble collagen as described in Example 3.

Figure 6 shows the release rate profile of various active ingredients from a single layer collagen film (thicknesses 0.01-3.0 mm) made from soluble collagen as described in Example 1A.

Figure 7 shows the measurement of protein concentration in samples taken from Costar Transwell Cells by three different methods: ELISA (closed circles); 125I labelled PDGF (open squares); and $^3$H-Thymidine uptake assay (closed squares).

Figure 8 shows the maximum height (MH) of granulation tissue at the advancing edges of the wound (light bars; units of mm) and approximate area and volume measurements for new granulation tissue were calculated (dark bars; units of mm$^3$), based on the assumption that the wounds healed concentrically and did not contract.

Figure 9 shows effects of PDGF on the wound breaking strength when compared to untreated animals in the gastric linear wound model.

## DETAILED DESCRITION OF THE INVENTION

The present invention relates to a collagen film comprising one or two rate controlling layers and one or more drug reservoir layers, said layers contacting each other in a stacked conformation such that the rate controlling layer is situated at one or both ends of the stack, with the proviso that each of said rate controlling layer contacts only one other layer, said other layer being a drug reservoir layer. Preferably, there is only one rate controlling layer, which is situated at one end of the stack.

Rate controlling layers can be produced from a solution of soluble collagen. Soluble collagen is collagen that has an average molecular weight of less than 400,000, preferably having a molecular weight of about 300,000. A particularly suitable soluble collagen is Semex S (Semex Medical Co., Malvern, Pennsylvania). This particular soluble collagen is also advantageous because it is the atelopeptide form of the collagen. Atelopeptide collagen is collagen that is free of telopeptide, which is a peptide located at one end of purified collagen often associated with immunogenicity. A solution of the telopeptide form of collagen can be converted to the atelopeptide form of collagen via hydrolysis using organic acid. Another preferred characteristic of the soluble collagen is that it possesses a minimal amount of crosslinking, i.e., 0.5% or less.

The soluble collagen can be dissolved in a suitable solvent such as water to produce a solution that contains from about 0.5 to about 10% of collagen by weight, preferably from about 1 to about 5% by weight, and more preferably about 2% by weight.

Rate controlling layers can also be produced from a dispersion of collagen fibrils in suspension. Collagen fibrils, which are commercially available (e.g., Vitaphore Co., Menlo Park, California), can be dispersed into a suitable solvent such as water to produce a suspension that contains from about 0.1 to about 10% of collagen by weight, preferably from about 1 to about 2% of collagen by weight. To aid in the dispersion of the collagen fibrils into the suspension, a suitable dilute acid can be present in the solvent. A particularly suitabl acid is acetic acid at a concentration of about 5%.

The various layers contact each other by any number of methods. One such method is to place layers adjacent to each other and apply pressure to the outer sides of the layers to force the layers together. Another method is to coat the surface of each of the layers to be contacted with a solvent, such as water, before placing the layers together. In this way, a thin portion of each surface will become soluble thereby producing adhesion upon contact. Another method is to use a known adhesive on one or more of the contacting surfaces. Preferably, the adhesive is one that will not interfere with the release of the active ingredient from a layer. The preferred method of contacting the layers is with the application of equal pressure on each of the layers to be contacted.

The number of drug reservoir layers is determined by the desired release characteristics. Generally, more layers produce a more steady and more sustained release of the active ingredient. Preferably, the number of drug reservoir layers is from 1 to 10, more preferably from 1 to 5 and most preferably from 1 to 3. The concentration of active ingredient in different layers can be varied and the thickness of the different layers need not be the same.

The rate controlling layer may be at one or both ends of the stack. A stack of layers with a rate controlling layer at only one end is particularly suited to deliver an active ingredient to an epidermal surface. A stack of layers with a rate controlling layer at both ends is particularly suited to deliver an active ingredient to an internal wound or to a two surfaced wound, such as a surgical incision.

When there is only one rate controlling layer at one end of the stack, the other end of the stack may optionally consist of a backing layer. Such a backing layer can be any of the conventionally known backing layers. Generally, the backing layer comprises polyurethanes.

The collagen films of the present invention are useful as a means of delivering the active ingredient to cells or tissue with which it is in contact. For example, in the treatment of burns or other traumas to the skin, a collagen film with one rate controlling layer and one backing layer can be placed on the wound to deliver a suitable active ingredient to the traumatized area. PDGF is a particularly suitable active ingredient for such uses. Collagen films with rate controlling layers at both ends of the stack can be used to accelerate healing of surgical wounds. When used in such a way, the film can be placed in the surgical incision and stitched into the wound as an interface between the two surgical wound surfaces. Collagen films can also be used to deliver neurotrophic factors. When used in such a manner, the collagen film can be placed in direct contact with or adjacent to the nerve tissue to be treated with the neurotrophic factor.

## EXAMPLES

The following examples are intended to exemplify specific embodiments of the present invention without limiting the scope in any way.

### Example 1: Preparation of a Single Layer Collagen Film.

#### A. Soluble Collagen.

Collagen films containing various growth factors were prepared by the solvent casting method from a solution of soluble collagen. The soluble collagen was purchased from Semex Co. (Frazer, Pennsylvania). This collagen is from bovine origin and it contains 99% type I collagen and 1% type III collagen. The molecular weight of the collagen is 300 K dalton and the density is 0.044 gram/cc. The antigenicity of the collagen is minimal since the telopeptide is removed from the collagen.

First, a collagen solution (about 1 to 8%) was prepared by dissolving the soluble collagen in 0-5% acetic acid solution at 18-70°C. After the addition of the plasticizer glycerol (about 20% of the dry weight of the collagen), ethanol was added to the solution to facilitate the solvent evaporation process. The amount of alcohol was about 20% of the amount of the solution. The solution is then centrifuged to remove the undissolved material.

A growth factor solution (with or without radioactive material) was added to the solution. The solution was cast on a Teflon™ surface and dried at room temperature until the weight of the film was constant (for about 1-3 days) to produce collagen films containing various amounts of growth factor. Table I shows the thickness of the films prepared from the different concentrations of the collagen solution. Figure 6 shows the release profiles of PDGF from the collagen films with the release profiles being obtained by using the methods of Example 4 for various single layer films.

one collagen layer (membrane A) was prepared by a solvent casting method from an aqueous solution containing soluble collagen (4% collagen in 10mM acetate buffer (pH 4) in 0.85% NaCl solution), glycerol (20% w/w of collagen), and ethanol (20% of the solution). The second film (membrane B) had almost the same thickness (0.01 - 3mm) and the same composition as the first film except it contained PDGF (20 $\mu g/cm^2$ film). The two films were combined into one by attaching them together by evenly applying pressure. *In vitro* release rate study conducted according to Example 4 showed that the growth factor was released at constant rate for more than 12 hours (Figure 4).

Example 3: Preparation of a Multiple Layer Collagen Film.

A three layer film or a four layer film was prepared to produce a long term delivery device of growth factors. In one example a four layer film was prepared by the following method. Four different castings were performed as in Example 1A and then the films were combined into one by attaching them together by evenly applying pressure. The thickness of each layer was similar (0.01-3mm) however, different thickness layers could be used. The first collagen layer which will contact the skin did not contain PDGF. The concentrations of PDGF were 0.07%, 0.15%, and 0.30% for the second, the third, and the fourth layers respectively. Subsequent release study showed that a nearly constant release rate of the growth factor was maintained up to 100 hours Figure 5. At that time, almost 90% of the growth factor was released.

Example 4: Measurement of Release Kinetics.

Release rates of active ingredients from collagen films was conducted using Coster Transwell Cells ("Cell") (Costar Co., Cambridge, Massachusetts) as follows. Collagen films were produced as described in Examples 1, 2 and 3, and wafers (1.6 cm diameter) were cut from the films. Each wafer was transferred to a Coster Transwell Cell and placed on top of the polycarbonate membrane. 2.5 ml of the receiver solution (water and 1% bovine serum albumin, or water and 0.25% human serum albumin) was added to the Cell holder. The Cells were set on the solution and the release study was initiated. At specified times, 20 $\mu$l of the receiver solution was pipetted out and the same amount of fresh solution was replaced in the receiver solution. The sampling procedure was repeated to get another 20 $\mu$l sample. The radioactivity of the sample was measured with a gamma counter (Beckman Instruments, Co., Irvine, California). The concentration of protein in the receiver solution at any given time was calculated based on the radioactivity and confirmed using other methods such as ELISA and $^3$H-thymidine uptake bioassays. Results obtained using this assay are shown in Examples 1, 2, and 3 for films of various layers and thicknesses (Figure 1 to 6). Figure 7 shows the agreement of the various methods of measuring protein concentration.

If films were prepared under the standard condition, and the solvent was removed completely under the same conditions, the diffusion coefficient should be independent of the thickness of the film. In general, the release profile of PDGF from the single layer collagen film can be described by the following equation.

$$F = 2.26 \times (D^{1/2}/L)\ T^{1/2}$$

wherein:

F = the fraction of the drug released at time T;
D = the diffusion coefficient of PDGF in the swollen film; and
L = the thickness of the swollen film.

The equation shows that the plot of F versus square root of time should be linear. A plot of F versus square root of time showed a linear relationship between the amount of PDGF released and the square root of time.

The diffusion coefficient (D) can be calculated from the slope of the plot and the thickness of the dry collagen film using the above equation. Such a calculation with film thickness of 0.05 mm gave a diffusion coefficient of $3 \times 10^{-9}$ cm$^2$/sec. This value was much smaller than the diffusion coefficient of PDGF in Geliperm membrane. Since the measurement of the swollen collagen film is difficult to measure accurately, the apparent diffusion coefficient (Da) has been defined as:

$$Da = D\ (Lo/L)^2$$

wherein D and L are defined as above and Lo is the thickness of the dry film. The apparent diffusion coefficient (Da) can be obtained from the slope of the plot of F versus square root of time using the equation

TABLE 3

| Volume of Tissue Generated ($mm^3$ + standard deviation) | | |
|---|---|---|
| Time (days) | Control | PDGF |
| 5 | 12.6 ± 10.1 | 31.8 ± 15.0 |
| 10 | 15.3 ± 9.8 | 165.9 ± 21.4 |
| 15 | 17.1 ± 10.7 | 209.0 ± 23.5 |

Example 6: Measurement of Wound Healing Using the Rabbit Ear Model.

This example measures the influence of growth factors in a collagen film on the rate of healing of surgically created 6mm diameter dermal ulcers in the rabbit ear. This excisional wound model replicates the healing parameters (i.e., minimal wound contraction, generation of new granulation tissue, reepithelialization) associated with full thickness dermal wounds such as human leg ulcers. The full thickness wound model permitted histiologic quantification of both reepithelialization and formation of granulation tissue while excluding wound contracture as a variable. In addition, since cartilage is avascular, and the perichondrium was removed during surgery, new granulation tissue and new epithelium arises solely from the periphery of the wound. PDGF was applied at the time of surgery.

A. Pre-operative Preparation

Young adult New Zealand White rabbits, weighing approximately 3.0 to 3.5 kg each (M & K Rabbitry, Bentonville, Arkansas) were anesthesized using Rompum® (Farbenfabriken, Bayer, West Germany) as a sedative, followed (10 minutes later) by ketamine (60 mg/kg) and xylaine (5 mg/kg), both administered intramuscularly. Each rabbit's weight was measured and recorded. A small cotton or gauze plug was inserted into both ears of each rabbit, after which the inner surface and outer edges of both ears were shaved using an animal clipper (#40 blade). Commercially available Neet® depilatory cream was then applied to the inner surface of each ear for 10 minutes, after which time it was removed with dry gauze. The inner surface of the ears was wiped with saline-soaked gauze followed by application of a 70% alcohol solution. The dermis of the inner surface on one ear of each rabbit was blanched by infiltration of the ear with a 2% xylocaine solution containing 1:1000 epinephrine (this requires 1.5 to 3.0 mls total volume) using a 30 gauge needle. The infiltrated area was then scrubbed with 3 cycles of betadine followed by the 70% alcohol solution. Where necessary, the ear plugs were replaced with dry plugs at this point.

The rabbits were then transferred to a sterile surgical room. The blanched ear was immobilized on a plexiglass "ear board" (Washington University Medical Center, Division of Technical Services, St. Louis, Missouri) which utilizes two bar clamps, one at the tip and one at the base of the animal's ear, to stabilize the rabbit ear without compromising its blood supply. The animal was draped, and the surgical field (i.e., the inner surface of the blanched ear) sprayed with Betadine and allowed to dry for 3 to 5 minutes.

B. Wounding

Sterile technique was employed thoughout the wounding procedure. Using microsurgical instruments, a 6 mm trephine, and a binocular microscope (10x, Zeiss), the surface of the inner ear of each rabbit was scored gently with a 6 mm biopsy punch, and the biopsy site cleared of all tissue and fibers (including the periosreal membrane) down to the level of bare cartilage, using micro-surgical forceps, tenotomy scissors, a blunt edged 2 mm Lempert periosreal elevator, and sterile cotton-tipped applicators. Perichondrium and overlying tissues were removed by dissection. Biopsies in which the cartilage was completely cut through by the punch were not used for experimental purposes. However, partial thickness scores of the cartilage were considered acceptable. The location of any nicks or natural holes in the cartilage was carefully noted and recorded (for reference on the harvest day) . Blood was removed from the biopsy site with sterile, cotton-tipped applicators, with care taken to avoid excess blood in the wound. Each completed biopsy was covered with a small piece of saline-soaked gauze. Four viable 6 mm biopsy ulcers were placed on each wounded ear, two on each side of the midline (as defined by the fold in the ear when it was stabilized upon the board). In any event, no more than 5 total biopsies were placed on each  ar. The biopsies were positioned a minimum of 1 cm apart.

GTG) from the day zero wound area (22.7 $mm^2$). India ink tatoos were placed at the wound periphery on day zero to assess the degree of contraction during healing. After 7 days, wound diameters were unchanged. Infected wounds (less than 5%) or desicated wounds (less than 5%) were excluded before measurements were made. Cultures of clinically noninfected wounds were repeatedly conducted and showed no growth of pathogens.

Nonparametric and parametric statistical analyses were carried out using SAS software. The resulting data are shown in Table 4. Similar experiments were performed using collagen wafer containing PDECGF. The resulting data for MH and the calculated volume of new granulation tissue is shown in Figure 8.

Farms, Bentonville, Arkansas) were preanesthetized by subcutaneous injection of atropine (0.1 mg/kg) and acepromazine (0.75 mg/kg). After a time span of 10 minutes, the animals were anesthetized with ketamine (0.75 mg/kg) and xylazine (5 mg/kg). Their abdomens were shaved with a #40 blade and sterilely prepared for surgery. A 10 cm midline laparotomy was made, the cecum was mobilized to expose the sacculus rotundus and approximately 20 cm of the cecum. Two haustra distal to the sacculus rotundus were counted off and paired 3 cm linear incisions were made parallel to the length of the cecum and 180 degrees opposite. Two more haustra were counted off the distal ends of the first two incisions and 2 or 3 cm incisions were made in like manner. To create a reproducible surgical plane, the incisions were carried through the serosal and muscular layers to leave the cecum mucosal layer intact. The collagen strips were then placed in the wound as to lay flat against the muscularis mucosae. The incisions were closed with a running 5-0 polypropylene suture (Ethicon Corp., Somerville, New Jersey) at five sutures per centimeter and two millimeters from the wound margin. Sutures were placed through the serosal, muscular, and sub-muscular layers so as to draw these layers up and over the collagen strip against the muscularis mucosae. At the final knotting of the suture, the loop was trimmed in the control wounds and left intact in the experimental wounds so as to remove any chance of error at time of harvesting.

Care was taken to rotate the experimental therapy and the vehicle alone (control) between the four wounds. The laparotomy incision was closed by layers in the standard fashion. The animals were fed a standard diet (Tekland Rabbit Chow, Illinois) and given water ad libitum and housed individually in a controlled environment. On a predetermined day the animals were humanely euthanized with pentobarbitol (150 mg/kg) injected intravenously into the marginal ear vein. The wounded section of cecum was excised and the contents thoroughly flushed.

The suture was atraumatically removed from each wound and three standardized 8 mm strips were cut across each incision with the use of a punch template (Washington University machine shop). Histological samples were taken from areas between the wound strips. Wound breaking strength was measured in grams/mm$^2$ on a tensometer (Tensometer 10, Monsanto, St. Louis, Missouri) on three strips from each incision (six experimental, six control/rabbit). If evidence of infection, hematoma, or poor coaptation were evident, the sample was disregarded (<2% of all wounds were disregarded from analysis). All wounds were tested on the tesometer at 20 mm/min with the use of electrical claw clamps to insure breaking at the wound site only. Tensometry analysis was divided into three categories: fundal tissue, antral tissue, and cecal tissue and the data reported individually for each.

Histological analysis was performed on matched samples from each group. Samples were sutured into micro-casettes and stored in formalin and hemotoxlin and eosin staining was performed at a later date. The histological samples were then examined for thickness, amount of granulation tissue, and signs of necrosis, and this data was recorded.

The results for secal tissue are shown in Figure 9.

## Claims

1. A collagen film comprising a first rate controlling layer and one or more drug reservoir layer, said layers contacting each other to form a stack such that the rate controlling layer is situated at one end of the stack, with the proviso that said rate controlling layer contacts only one other layer, said other layer being a drug reservoir layer.

2. A collagen film according to claim 1 wherein said rate controlling layer comprises collagen and an active ingredient.

3. A collagen film according to claim 2 wherein said rate controlling layer is void of any active ingredient.

4. A collagen film according to claim 3 wherein each of said drug reservoir layer comprises collagen and an active ingredient.

5. A collagen film according to claim 4 wherein the number of said drug reservoir layers is from one to five.

6. A collagen film according to claim 5 wherein the number of said drug reservoir layers is from one to three.

7. A collagen film according to claim 6 wherein the number of said drug reservoir layers is three.

each independently have a thickness of from about 0.01 to about 1 mm.

30. A collagen film according to claim 29 wherein said rate controlling layer and said drug reservoir layer each independently have a thickness of from about 0.05 to about 0.5 mm.

31. A collagen film according to claim 30 wherein said rate controlling layer and said drug reservoir layer each independently have a thickness of from about 0.01 to about 0.2 mm.

32. A collagen film according to claim 31 wherein said rate controlling layer further comprises a plasticizer.

33. A collagen film according to claim 32 wherein said drug reservoir layer further comprises a plasticizer.

34. A collagen film according to claim 33 wherein said rate controlling layer further comprises a stabilizing agent.

35. A collagen film according to claim 34 wherein said drug reservoir layer further comprises a stabilizing agent.

36. A collagen film according to claim 34 wherein said rate controlling layer further comprises a drying enhancer.

37. A collagen film according to claim 35 wherein said drug reservoir layer further comprises a drying enhancer.

38. A collagen film according to claim 36 wherein said rate controlling layer further comprises a buffer.

39. A collagen film according to claim 37 wherein said drug reservoir layer further comprises a buffer.

40. A collagen film according to claim 38 wherein said active ingredient is selected from the group consisting of PDGF, EGF, FGF, PDEGF, PD-ECGF, KGF, IGF-1, IGF-2, and TNF.

41. A collagen film according to claim 39 wherein said active ingredient is PDGF.

42. A method of enhancing wound healing of an internal wound comprising administration of a wound healing effective amount of an active ingredient via a collagen film according to claim 22.

43. A collagen film comprising one or more drug reservoir layer, said layers contacting each other to form a stack of said drug reservoir layers.

44. A method of enhancing wound healing of an epidermal wound comprising administration of a wound healing effective amount of an active ingredient via a collagen film according to claim 42.

45. A method of enhancing wound healing of an internal wound comprising administration of a wound healing effective amount of an active ingredient via a collagen film according to claim 42.

FIG. 2

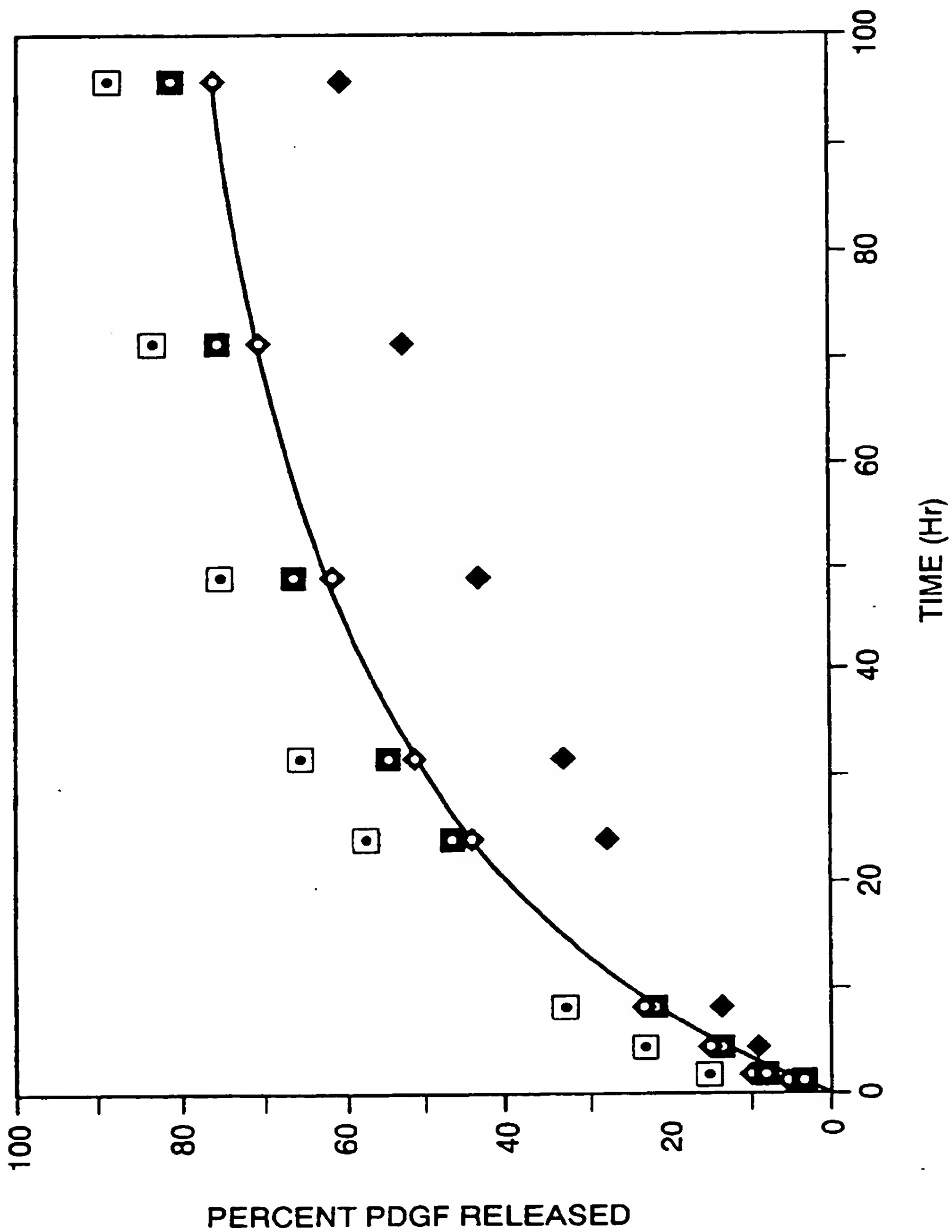


FIG. 4

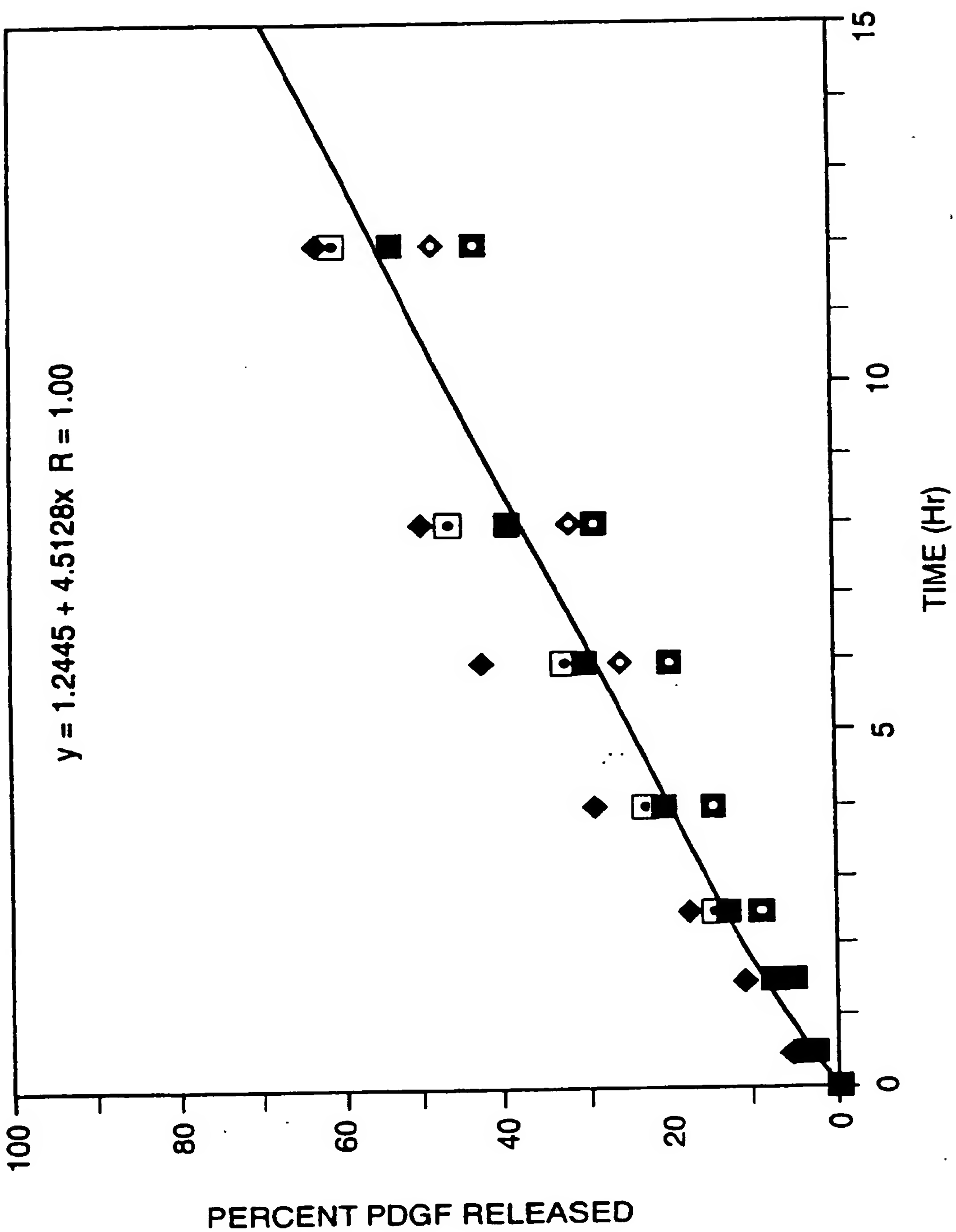

y = 1.2445 + 4.5128x R = 1.00
PERCENT PDGF RELEASED
0
20
40
60
80
100
TIME (Hr)
0
5
10
15

FIG. 6

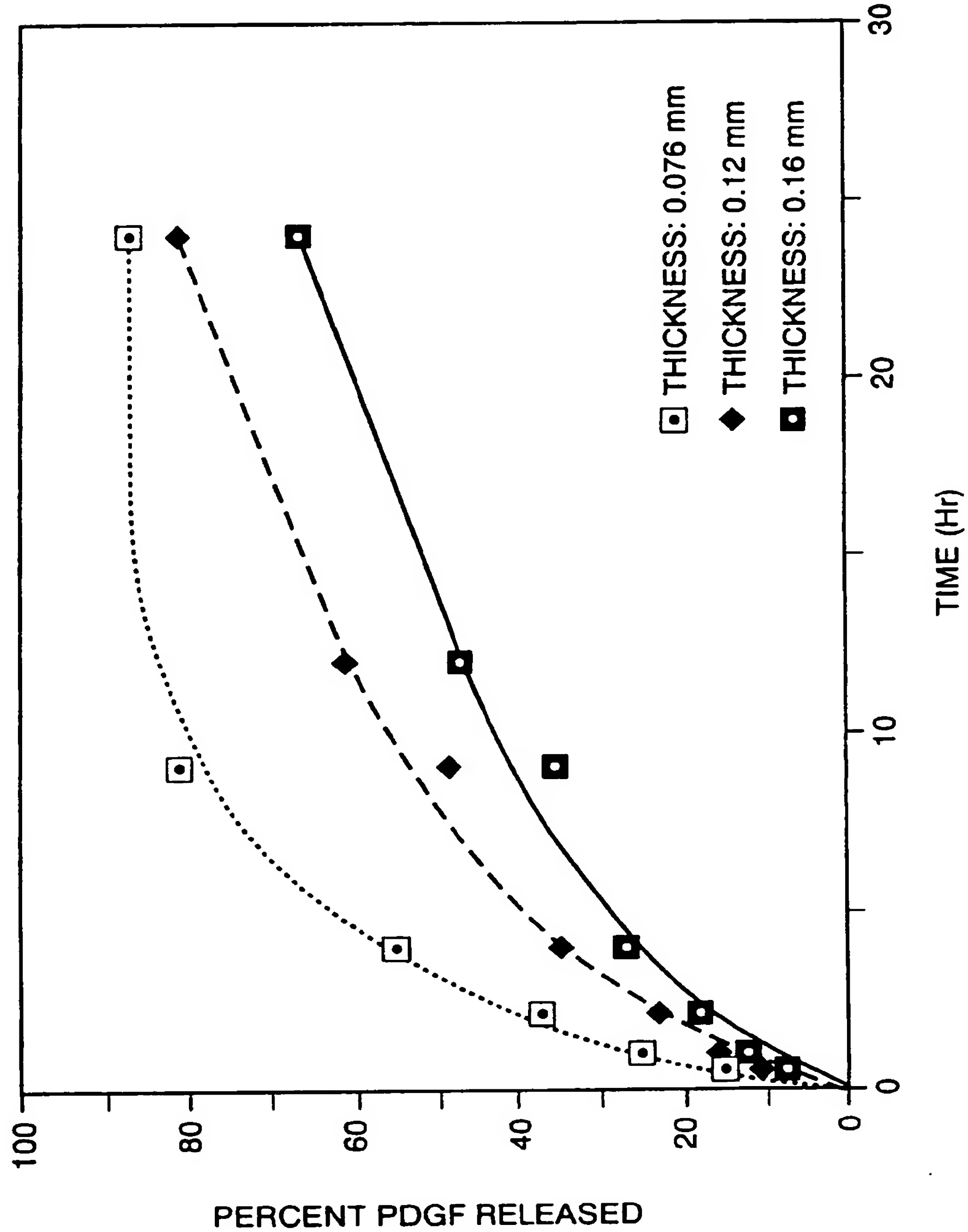
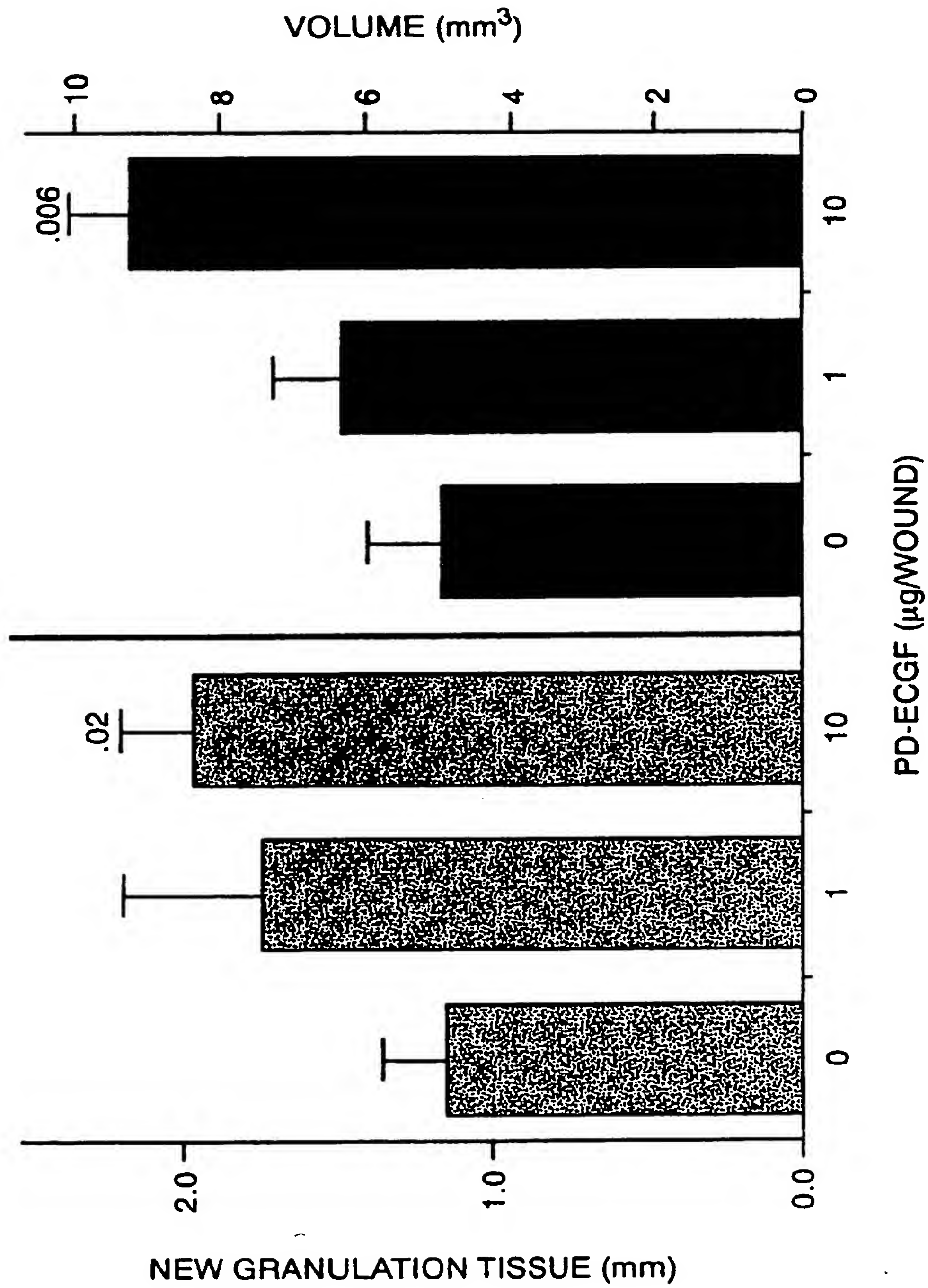

THICKNESS: 0.076 mm
THICKNESS: 0.12 mm
THICKNESS: 0.16 mm
PERCENT PDGF RELEASED
TIME (Hr)
0
10
20
30
0
20
40
60
80
100

FIG. 8


VOLUME (mm3)
10
8
6
4
2
0
.006
.02
10
1
0
10
1
0
PD-ECGF (µg/WOUND)
2.0
1.0
0.0
NEW GRANULATION TISSUE (mm)

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## (54) Collagen film for sustained delivery of proteins.

(57) The present invention relates to single and multiple layer collagen films that are useful for improved sustained release delivery of pharmaceuticals.

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